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EXAMINER	
BERTAGNA, ANGELA MARIE	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,975	MITANI ET AL.	
	Examiner	Art Unit	
	ANGELA BERTAGNA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☒ Claim(s) *12* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/15/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 15, 2009 has been entered.

Claims 1-17 are currently pending. In the response, claims 1, 3, and 9 were amended.

The following include new grounds of rejection necessitated by Applicant's amendment. Any previously made rejections not reiterated below have been withdrawn as being obviated by the amendment. Applicant's arguments filed on July 15, 2009 that remain pertinent to the new grounds of rejection have been fully considered, but they were not persuasive for the reasons set forth in the "Response to Arguments" section.

Information Disclosure Statement

2. Applicant's submission of an Information Disclosure Statements on July 15, 2009 is acknowledged. A signed copy is enclosed. Non-patent literature citations 1, 2, and 8 have not been considered, because their citations do not comply with 37 CFR 1.98(b)(5), which requires a date of publication.

Claim Objections

3. Claim 12 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 12 fails to further limit the method of claim 9, because claim 9 already recites that steps (a) – (c) of the method are conducted under isothermal conditions.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-7 and 9-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63; cited previously) and further in view of Nagamine (Molecular and Cellular Probes (June 2002) 16(3):223-229; cited previously).

These claims are drawn to an isothermal nucleic acid amplification method.

Regarding claim 1, Rabbani teaches a method for amplifying a nucleic acid comprising:

(a) annealing a primer to a template nucleic acid and synthesizing a complementary nucleic acid via primer extension,

wherein the primer comprises in its 3' end portion a sequence (Ac') that hybridizes to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5' of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of sequence (A) in the target nucleic acid (see Example 1 on page 21, especially paragraphs 120-121, where the FC and RC primers of Rabbani are taught; see also Figure 1, steps 1-2)

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 19 or 20 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20)

(b) hybridizing sequence (B') with sequence (Bc) on the newly synthesized strand, thereby allowing sequence (A) on the target strand to be single-stranded (see Figure 1, step 3)

(c) annealing another primer of step (a) to the single-stranded sequence (A) on the target generated in step (d) and conducting a strand displacement reaction, thereby displacing the complementary nucleic acid synthesized in step (c) (see Figure 1, steps 4-5).

Regarding claim 2, Rabbani teaches that the double-stranded nucleic acid obtained in step (e) is used repeatedly in step (d) (see Figure 1 and paragraph 47).

Regarding claims 1, 3, 9, and 12, Rabbani teaches that the method is conducted isothermally (see paragraphs 46, 51, and 121). Also, the primers used by Rabbani have a length within the claimed range of 15-100 nucleotides (see Example 1 on page 21, where the FC and RC primers of Rabbani have lengths within the claimed range).

Regarding claims 4 and 13, Rabbani teaches use of the Bst DNA polymerase, which has strand-displacing ability (paragraph 120).

Regarding claims 5 and 14, Rabbani teaches that the method further comprises a step of synthesizing cDNA with a reverse transcriptase from an RNA template (paragraph 111).

Regarding claims 6, 7, 15, and 16, Rabbani teaches conducting the method in the presence of a melting temperature adjusting agent, specifically formamide or DMSO (see paragraph 39).

Regarding claim 9, Rabbani teaches a method for amplifying a target nucleic acid in a double-stranded template nucleic acid comprising:

(a) annealing first and second primers to first and second template nucleic acids of a double-stranded template nucleic acid and synthesizing first and second complementary strands via primer extension (see paragraphs 117-118; see also Figure 1, steps 1-2 for a schematic of how the primers anneal to the target. Although Figure 1 shows the reactions occurring on only

one strand, when both the FC and RC primer are used with a double-stranded template as taught by Rabbani in Example 1, each of the primers inherently undergoes the reactions outlined in Figure 1 on a different strand of the template; see also paragraph 77, where Rabbani expressly teaches conducting the amplification method using two stem-loop primers each of which is complementary to a different strand of a double-stranded DNA template),

wherein the first primer comprises in its 3' end portion a sequence (Ac') that hybridizes to a sequence (A) in the 3'end portion of the target nucleic acid, and a sequence (B') located 5' of (Ac') that hybridizes to the complementary sequence (Bc) of a sequence (B) positioned 5' of sequence (A) in the target nucleic acid (see Example 1 on page 21, where the FC and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target; paragraphs 77 & 177 teach the use of double-stranded nucleic acid targets), and

wherein in the absence of an intervening sequence between (Ac') and (B'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Ac') and Y is the number of bases in the region flanked by sequences (A) and (B) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Ac') region of 19 or 20 nucleotides and the region flanked by sequences A and B is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20), and

wherein the second primer comprises in its 3' end portion a sequence (Cc') that hybridizes to a sequence (C) in the 3'end portion of the target nucleic acid, and a sequence (D') located 5' of (Cc') that hybridizes to the complementary sequence (Dc) of a sequence (D) positioned 5' of sequence (C) in the target nucleic acid (see Example 1 on page 21, where the FC

and RC primers of Rabbani are taught; see also Figure 1 for a schematic of the primers binding to a target)

wherein in the absence of an intervening sequence between (Cc') and (D'), (X-Y)/X is between –1.00 and 1.00, where X is the number of bases in sequence (Cc') and Y is the number of bases in the region flanked by sequences (C) and (D) on the target nucleic acid sequence (see Example 1 on page 21, paragraphs 117-118, where the FC and RC primers have an (Cc') region of 19 or 20 nucleotides and the region flanked by sequences C and D is 0 nucleotides, since there is no intervening sequence between them. Therefore, (X-Y)/X = 1 and X+Y = 19 or 20)

(b) hybridizing the sequences (B') and (D') with the newly synthesized sequences (Bc) and (Dc), respectively, thereby making sequences (A) and (C) single stranded (see Figure 1, step 3 and paragraph 118; see also paragraph 77)

(c) annealing primers having the same sequence as the first and second primers of step (a) to sequences (A) and (C) obtained in step (e) above and conducting strand displacement polymerization to displace the complementary strands obtained in step (d) and synthesize new complementary strands (see paragraph 118 and Figure 1, steps 4-5; see also paragraph 77).

Regarding claim 10, Rabbani teaches that the double-stranded nucleic acids obtained in step (f) are repeatedly used in step (e) (see paragraphs 77 & 118; see also Figure 1).

Regarding claim 11, Rabbani teaches that the first and second complementary nucleic acids obtained in step (f) as single-stranded nucleic acids are used repeatedly as template nucleic acids in step (d) (see Figure 2, step 4 and paragraph 77).

In the method of Rabbani, the FC and RC primers have an X value of 19 or 20, which lies within the range of 10-30 recited in independent claims 1 and 9 (see page 21). The FC and RC

primers of Rabbani also have an X+Y value of 19 or 20 (see page 21). This value lies outside of the range of 30-50 recited in independent claims 1 and 9. Also, in the method of Rabbani, the FC and RC primers have a value of X-Y/X = 1, which lies outside of the range recited in independent claims 1 and 9 (*i.e.* -1.00 to 0.75).

Notomi teaches a method for isothermally amplifying DNA using primers (FIP and BIP) that form stem-loop structures after extension (see abstract, pages ii-iv, and Figure 1). Like the primers of Rabbani, the FIP and BIP primers of Notomi comprise a region that is complementary to the template and a region that is complementary to a portion of the primer extension product (see pages ii-iv and Figure 1). Regarding claims 1 and 9, Notomi teaches that the size of the loop formed between the FIP or BIP primer and the primer extension product, which corresponds to the recited Y value, is critical to the efficiency of the amplification method, and that a loop of 40 bases or longer gave the best results (page v, column 1). Notomi also teaches that the FIP and BIP primers used in the method have an intervening sequence, which corresponds to the recited Y' parameter, located between the (Ac') and the (B') regions of the primer (see page ii, column 1, where an intervening sequence that is four nucleotides in length is taught). In the method of Notomi, the FIP and BIP primers have a template complementary region (*i.e.* an X value) of approximately 22-24 nucleotides (see page ii). Thus, the loop mediated amplification reaction Notomi utilizes primers having an X+Y value of 76 and 78 and an X-(Y-Y')/X value of -0.96 and -1.18 (see page ii and Figure 2A on page iv). The X-(Y-Y')/X value of -0.96 taught by Notomi lies within the claimed range of -1.00 to 0.75. The other X-(Y-Y')/X value and the values of X+Y+Y' taught by Notomi lie outside of the claimed ranges.

Nagamine teaches methods of conducting loop mediated isothermal amplification (see abstract and pages 224-225). Regarding claims 1 and 9, the method of Nagamine utilizes primers (FIP and BIP) having a 3' region that is complementary to the template nucleic acid and a 5' region that is complementary to a portion of the extension product generated upon extension of the 3' region of the primer (see pages ii-iv and Figure 1). The FIP and BIP primers used in the method of Nagamine have X+Y values that fall within the claimed range (see pages 224-225 and Figure 1, where the FIP and BIP primers of Nagamine have X+Y values of 43 and 45, respectively, and X-Y/X values of 0.35 and 0.20, respectively).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to apply the teachings of Notomi and Nagamine to the method taught by Rabbani. An ordinary artisan would have been motivated to optimize the length of the loop formed by the primer taught by Rabbani, since Notomi taught that this parameter was critical to achieving optimal amplification efficiency (page v, column 1). An ordinary artisan would have recognized from the teachings of Notomi that the length of the template-complementary portion of the primer (*i.e.* the recited X value), the length of the loop formed by the primer with the extension product generated during polymerase-mediated primer extension (*i.e.* the recited Y value) and the length of any intervening sequence these regions of the primer (*i.e.* the recited Y' value) were results-effective variables, the optimization of which was critical to practice of the method of Rabbani. Therefore, an ordinary artisan would have been motivated to perform routine experimentation to determine the optimal ranges for these parameters with a reasonable expectation of success. As noted in MPEP 2144.05, citing *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955), "[W]here the general conditions of a claim are disclosed in the

prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." An ordinary artisan would have been particularly motivated to select values of X and Y giving X+Y and X-Y/X values within the claimed ranges, since Nagamine taught that primers having X+Y and X-Y/X values within the claimed ranges were useful for performing loop-mediated isothermal amplification reactions, such as those taught by Rabbani and Notomi (see pages 224-225). Thus, the methods of claims 1-7 and 9-16 are *prima facie* obvious over Rabbani in view of Notomi and further in view of Nagamine.

5. Claims 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rabbani et al. (EP 0 971 039 A2; cited previously) in view of Notomi et al. (Nucleic Acids Research 2000; 28(12): e63; cited previously) and further in view of Nagamine (Molecular and Cellular Probes (June 2002) 16(3):223-229; cited previously) and further in view of Kool, E.T. (Current Opinion in Chemical Biology (2000) 4: 602-608; cited previously).

The combined teachings of Rabbani, Notomi, and Nagamine result in the methods of claims 1-7 and 9-16, as discussed above.

Rabbani, Notomi, and Naganine do not teach that target nucleic acid sequence in the template nucleic acid comprises non-natural nucleotides as required by claims 8 and 17.

Kool teaches methods of using modified DNA templates as substrates for DNA polymerases. Kool teaches that DNA polymerases can accept synthetic modifications to the template or newly synthesized strand (page 602, column 2). Kool further teaches that templates containing nucleotides with altered hydrogen-bonding capabilities may be amplified by DNA polymerase (page 604). Kool teaches that the presence of these non-native nucleotides in the

template strand directs non-specific incorporation of any of the four natural bases into the newly synthesized strand, which is useful for mutagenesis (page 604).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to conduct the amplification method resulting from the combined teachings of Rabbani, Notomi, and Nagamine using a template containing non-natural nucleotide. An ordinary artisan would have been motivated to do so, because Kool taught that the inclusion of such nucleotides in the template strand was useful for mutagenesis applications (see page 604). Since Kool further taught a number of specific examples of non-native nucleotides that could be recognized and amplified by DNA polymerases (see pages 604-606), an ordinary artisan would have had a reasonable expectation of success in utilizing a template containing non-native nucleotides in the method resulting from the combined teachings of Rabbani, Notomi, and Nagamine. Thus, the methods of claims 8 and 17 are *prima facie* obvious over Rabbani in view of Notomi and further in view of Nagamine and further in view of Kool.

Response to Amendment

6. The declaration filed under 37 CFR 1.132 on July 15, 2009 is insufficient to overcome the rejection of claims 1-7 and 9-16 under 35 U.S.C. 103(a) based upon the combined teachings of Rabbani, Notomi, and Nagamine and the rejection of claims 8 and 17 under 35 U.S.C. 103(a) based on the combined teachings of Rabbani, Notomi, Nagamine, and Kool as set forth in the last Office action, because the evidence presented in the declaration does not clearly establish that the differences in amplification specificity and efficiency observed in primers having the

claimed features are unobvious and of statistical significance. The evidence presented in the declaration also is not commensurate in scope with the claimed invention.

As noted in MPEP 716.02 citing *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986), "Any differences between the claimed invention and the prior art may be expected to result in some differences in properties. The issue is whether the properties differ to such an extent that the difference is really unexpected." MPEP 716.02(a) further adds that "Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." Similarly, MPEP 716.02(b) states that "The evidence relied upon should establish 'that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.' *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992)."

In this case, the data presented in the declaration filed on July 15, 2009 show that three primer sets satisfying all of the claimed requirements (*i.e.* X between 10 and 30, X+Y between 30 and 50, and X-Y/X between -1.00 and 0.75) show increased amplification efficiency and specificity compared to six sets of primers that satisfy some or none of the above requirements (see page 6 of the declaration). However, the data does not establish that the observed improvements are due to the fact that the primers satisfy the claimed conditions. In other words, the declaration does not establish what would be considered a "baseline" for amplification efficiency and specificity and then demonstrate that primers having the claimed features show an unobvious and unexpected improvement in amplification specificity and efficiency relative to the baseline. In the absence of such a baseline, it is impossible to determine what results might

reasonably be expected from routine optimization of the claimed parameters, which as noted above, were known in the art to be results-effective variables. As a result, the declaration fails to establish that the observed results were, in fact, unexpected, unobvious, and statistically significant.

The evidence presented in the declaration is also not commensurate in scope with the claimed invention. As noted in MPEP 716.02(d), "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the 'objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support.' In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980)." MPEP 716.02(d) also states that "The nonobviousness of a broader claimed range can be supported by evidence based on unexpected results from testing a narrower range if one of ordinary skill in the art would be able to determine a trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof. *In re Kollman*, 595 F.2d 48, 201 USPQ193 (CCPA 1979)." In this case, the data presented in the declaration only addresses primer sets where there is not an intervening sequence, Y', between primer regions Ac' and B'. As a result, the data does not contain any results for amplification primers having X values between 10 and 30, X+Y+Y' values between 30 and 50, and (X-(Y-Y'))/X values between -1.00 and 0.75. The addition of the intervening sequence Y' will necessarily alter the range of possible values for X and Y that will still result in the primers satisfying the claimed conditions. This alteration in X and Y may result in reduction or elimination of the improvements in amplification specificity and efficiency observed with

primers lacking the intervening sequence Y'. The addition of an intervening sequence will also affect the properties of the resulting primers (*e.g.* by altering their conformational flexibility and the thermostability of any hybrids formed between the primers and their complementary sequences). These changes may also result in reduction or elimination of the improvements in amplification specificity and efficiency observed with primers lacking the intervening sequence Y'. As a result, it cannot be reasonably determined from the data presented in the declaration that the observed results regarding amplification specificity and efficiency in primers lacking an intervening sequence Y' would necessarily extend to primers having the intervening sequence.

Finally, as noted in MPEP 716.02(c), "Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a final determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978).... Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of *obviousness*. In re Nolan, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977)." In this case, as discussed above, the prior art of Notomi taught that the factors corresponding to X, Y, and Y' should be optimized using routine experimentation to determine the optimal values (page v, column 2). Also, the prior art of Nagamine taught the use of primers having the disclosed features in an isothermal amplification method. As a result, the prior art of Notomi and Nagamine would have suggested performing routine optimization of the analogous features in the primers of Rabbani, which have the same features (*i.e.* a 3' target-specific portion and a 5' region that hybridizes to a region of the product synthesized during extension of the primer located 5' of the region of the template hybridized by

the primer). An ordinary artisan would have had a reasonable expectation of success in obtaining and using primers having X and Y values within the claimed ranges, since Nagamine taught that primers having such features were useful in a similar isothermal amplification method. Based on these teachings in the art, it must be concluded that the evidence of unexpected results is not stronger than the evidence of obviousness, particularly in view of the fact that the declaration does not establish that the observed results are unexpected.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. Accordingly, the rejections made under 35 U.S.C. 103(a) citing Rabbani, Notomi, and Nagamine as the primary combination of references have been maintained.

Response to Arguments

7. Applicant's arguments filed on July 15, 2009 have been fully considered, but they were not persuasive.

Regarding the rejection of claims 1-7 and 9-16 under 35 U.S.C. 103(a) as being unpatentable over Rabbani in view of Notomi and further in view of Nagamine, Applicant first argues that the claimed methods are unobvious in view of the declaration submitted under 37 CFR 1.132 (see pages 7-11). This argument was not persuasive, because as discussed above, the declaration was insufficient to overcome the rejection.

Applicant also argues that Notomi and Nagamine expressly teach that the disclosed isothermal amplification method (LAMP) requires the use of six distinct nucleic acid binding sites for primer design, and therefore, the reference leads away from applying the teachings

present therein to the method of Rabbani, which does not require the use of six distinct primer binding sites in the target (see pages 11-12). In response to this argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, as discussed above, the primers of Notomi, Nagamine, and Rabbani each comprise a 3' target-specific portion and a 5' non-complementary portion that binds to a portion of the extended product (see Figure 1 of Rabbani and Figure 1 of Notomi). Accordingly, an ordinary artisan would have been motivated to apply the teachings of Notomi and Nagamine regarding optimizing the lengths of these regions to the primers of Rabbani with a reasonable expectation of success.

It is also noted that the Notomi and Nagamine references are not nonanalogous art as argued by Applicant (see pages 11-12). It has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, the Notomi and Nagamine references were in the field of Applicant's endeavor (*i.e.* isothermal nucleic acid amplification) and also reasonably pertinent to the problem with which Applicant was concerned (*i.e.* isothermal nucleic acid amplification using primers having a 3' target-complementary region and a 5' region that hybridizes to a region of the newly

synthesized primer extension product). Thus, the Notomi and Nagamine references are not nonanalogous art.

Finally, it is further noted that neither the Notomi reference nor the Nagamine reference actively disparages, discredits, or discourages the use of other lengths for the regions corresponding to the claimed X and Y values (see MPEP 2123 and 2145). Furthermore, as discussed above, the teachings of Nagamine (see pages 224-225) would have suggested to the ordinary artisan the use of primers having X and Y values that produced X+Y and X-Y/X values within the claimed ranges.

Regarding the rejection of claims 8 and 17 under 35 U.S.C. 103(a) as being anticipated by Rabbani in view of Notomi and further in view of Nagamine and further in view of Kool, Applicant argues that the teachings of Kool do not remedy the deficiencies of the primary combination of references (*i.e.* Rabbani, Notomi, and Nagamine) with respect to independent claims 1 and 9 (see page 12). This argument was not persuasive, because as discussed above, the combined teachings of Rabbani, Notomi, and Nagamine render obvious the methods of claims 1-7 and 9-16. Since Applicant's arguments were not persuasive, the rejection has been maintained.

Conclusion

8. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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